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NEW IMIDAZOLE DERIVATIVES OR THEIR MINERAL ACID SALTS AND PREPARATION METHOD THEREOF

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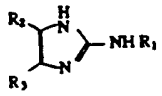
[There are no amendments to this patent.]

Claims

1. New imidazole derivatives or their mineral acid salts expressed by the following formula (1)



..... (1)

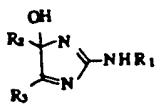
where R_1 is a substitutable C_{1-8} alkyl, aryl or aralkyl, and R_2 and R_3 are the same or different substitutable aryls.

2. New imidazole derivatives or their mineral acid salts as described in Claim 1 wherein R_1 in the formula (1) is methyl, ethyl, isopropyl, benzyl, or substituted benzyl.

3. New imidazole derivatives or their mineral acid salts as claimed in Claim 1 or 2 wherein R_2 and R_3 in the formula (1) are phenyl, tolyl, p-chlorophenyl, or p-methoxyphenyl.

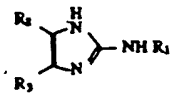
4. Mineral acid salts of new imidazole derivatives as claimed in Claims 1-3 wherein the mineral acid salts are hydrochloric acid salts or nitric acid salts.

5. A preparation method of new imidazole derivatives or their mineral acid salts expressed by the following formula (1)



..... (2)

where R_1, R_2, and R_3 are the same as above,
characterized in that compounds expressed by the formula (2)



..... (1)

where R_1 is a substitutable C_{1-8} alkyl, aryl or aralkyl, and R_2 and R_3 are the same or different substitutable aryls, are hydrogenated in the presence of catalysts and. if necessary, treated with mineral acids.

6. The preparation method as claimed in Claim 5 wherein the catalysts are platinum oxide, palladium-carbon, and Raney nickel.

Detailed explanation of the invention

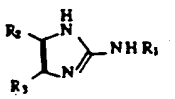
The present invention relates to new imidazole derivatives or their mineral acid salts and their preparation method. More specifically, the present invention relates to new imidazole derivatives or their mineral acid salts useful as medicines and their preparation method.

Known imidazole derivatives useful as medicines include 2-substituted thio-4,5-diphenylimidazole which shows anti-inflammation activity (refer to Japanese Kokai Patent Application No. Sho 52[1977]-23076), and imidazole and benzimidazole derivatives show antiulcer characteristics (refer to Japanese Kokai Patent Application No. Sho 18831).

In addition, it is known that 2-substituted aminobenzimidazole derivatives show antiviral activity, insect extermination activity, and anti-inflammation action (refer to U.S. Patent Nos. 4,002,623, 4,004,016, 4,018,790, 4,008,243, and 4,025,638).

The present inventors have assiduously conducted a study to develop new imidazole derivatives by considering imidazole derivatives having physiological activity so as to be useful as medicines and, as a result, have found that new 2-substituted amino-4,5-diarylimidazoles and their mineral acid salts show anti-inflammatory activity, and thereby the present invention was completed.

Namely, the present invention provides new imidazole derivatives or their mineral acid salts expressed by the following formula (1)



..... (1)

where R_1 is a substitutable C_{1-8} alkyl, aryl or aralkyl, and R_2 and R_3 are the same or different substitutable aryls. In formula (1), R_1 is a substitutable C_{1-8} alkyl, aryl or aralkyl, and R_2 and R_3 are the same or different substitutable aryls as defined above.

As the C_{1-8} alkyl for R_1, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, etc., may be exemplified, and as the aryl for R_1, R_2 and R_3, phenyl, o-, m-, or p-tolyl, pyridyl, o-, m-, or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m, or p-methoxyphenyl, etc., may be exemplified, and in addition as the aralkyl for R_1, benzyl may be exemplified. In addition, as substitution radicals for these, for instance, halogen atoms such as fluorine, chlorine, bromine, etc., are preferable.

Among the aforementioned compounds of this invention, however, compounds having methyl, ethyl, isopropyl, benzyl, or substituted benzyl as R_1 or compounds having phenyl, tolyl, p-chlorophenyl, or p-methoxyphenyl as R_2 and R_3 are particularly preferred.

Concrete compounds of new imidazole derivatives expressed by formula (1) of this invention are illustrated as follows:

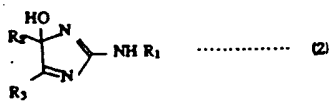
2-methylamino-4,5-diphenylimidazole, 2-ethylamino-4,5-diphenylimidazole,
2-isopropylamino-4,5-diphenylimidazole, 2-benzylamino-4,5-diphenylimidazole,
2-methylamino-4,5-di(p-chlorophenyl)imidazole, 2-methylamino-4,5-di(p-tolyl)imidazole,
2-methylamino-4,5-di(p-fluorophenyl)imidazole, 2-ethylamino-4,5-di(p-chlorophenyl)imidazole,
2-ethylamino-4,5-di(p-methoxyphenyl)imidazole, 2-ethylamino-4,5-di(p-tolyl)imidazole,
2-(p-chlorobenzylamino)-4,5-diphenylimidazole,
2-(o-chlorobenzylamino)-4,5-diphenylimidazole,
2-(m-chlorobenzylamino)-4,5-diphenylimidazole,
2-(p-chlorobenzylamino)-4,5-di(p-tolyl)imidazole,
2-(o-chlorobenzylamino)-4,5-di(p-tolyl)imidazole,
2-(m-chlorobenzylamino)-4,5-di(p-tolyl)imidazole,
2-(p-chlorobenzylamino)-4,5-di(p-chlorophenyl)imidazole,
2-(o-chlorobenzylamino)-4,5-di(p-chlorophenyl)imidazole,
2-(m-chlorobenzylamino)-4,5-di(p-chlorophenyl)imidazole,
2-(p-chlorobenzylamino)-4,5-di(p-methoxyphenyl)imidazole,
2-(o-chlorobenzylamino)-4,5-di(p-methoxyphenyl)imidazole,
2-(m-chlorobenzylamino)-4,5-di(p-methoxyphenyl)imidazole,
2-(p-methoxybenzylamino)-4,5-diphenylimidazole,
2-(o-methoxybenzylamino)-4,5-diphenylimidazole,
2-(m-methoxybenzylamino)-4,5-diphenylimidazole,
2-(p-methoxybenzylamino)-4,5-di(p-tolyl)imidazole,

2-(o-methoxybenzylamino)-4,5-di(p-tolyl)imidazole,
2-(m-methoxybenzylamino)-4,5-di(p-tolyl)imidazole,
2-(p-methoxybenzylamino)-4,5-di(p-chlorophenyl)imidazole,
2-(o-methoxybenzylamino)-4,5-di(p-chlorophenyl)imidazole,
2-(m-methoxybenzylamino)-4,5-di(p-chlorophenyl)imidazole,
2-(p-methoxybenzylamino)-4,5-di(p-methoxyphenyl)imidazole,
2-(o-methoxybenzylamino)-4,5-di(p-methoxyphenyl)imidazole,
2-(m-methoxybenzylamino)-4,5-di(p-methoxyphenyl)imidazole,
2-(2,4-dichlorobenzylamino)-4,5-diphenylimidazole, 2-phenylamino-4,5-diphenylimidazole,
2-methyl-4(5)-tolyl-5(4)-phenylimidazole,
2-methylamino-4(5)-(p-methoxyphenyl)-5(4)-phenylimidazole, etc., may be exemplified, but the compounds are not limited to these.

In addition, mineral acid salts, especially hydrochloric acid salts or nitric acid salts, of these compounds are preferable compounds in this invention.

New imidazole derivatives or their mineral acid salts expressed by formula (1) of this invention can be prepared as follows.

Namely, compounds expressed by the following formula (2)



..... (2)

[In the formula, R_1, R_2, and R_3 are the same as the definitions mentioned above.]
are hydrogenated in the presence of catalysts and, if necessary, treated with mineral acids to prepare new imidazole derivatives of formula (1) or their mineral acid salts.

The present invention reaction is carried out generally in the presence of organic solvents. As such organic solvents, for instance, alcohols, halogenated hydrocarbons, and esters may be exemplified, and among those methanol is preferably used. As the catalysts, for instance, platinum oxide, palladium-carbon, and Raney nickel, etc., are preferably used. A suitable amount of catalyst is 1-5 wt% of the compounds expressed by formula (2).

The reaction temperature and reaction time vary with types and quantities of raw materials and catalyst. etc., but are generally 0-70°C, preferably 0-25°C, and 3-24 h, respectively.

After completing the reduction, the catalyst is removed by filtering, and the reaction solution is concentrated, allowed to stand or dried to a solid, and recrystallized from a suitable solvent such as methanol, ethanol, isopropanol, n-butanol, dimethyl formamide, water-containing alcohols, or mixed solvents of alcohols and ethers to separate a desired

compound as a free base. In addition, a suitable amount of mineral acid is added to the reaction solution after reaction, and then this is concentrated, allowed to stand or dried to a solid, and recrystallized from a suitable solvent to separate a corresponding mineral salt.

Hydrochloric and nitric [acids] are suitable for this purpose.

Hereafter the present invention will be explained in detail using application examples.

Application Example 1

Preparation of 2-methylamino-4,5-diphenylimidazole

2.65 g 2-Methylamino-4,5-diphenyl-4-hydroxy-4H-imidazole (10 mM) and 5% 1.20 g palladium carbon were suspended in 30 mL methanol, stirred under hydrogen gas at 1 atm and room temperature until the absorption of hydrogen gas stopped (about 4 h), filtered to separate the catalyst, and the filtrate was concentrated and dried to a solid. The residue was supplemented with 6 mL isopropanol and allowed to stand. The produced precipitate was separated by filtering, washed twice with the same solvent, and air dried to obtain a light yellow powder. Yield 1.12 g. Melting point 189-196°C. The mother liquor was concentrated, dried to a solid, supplemented with 2 mL chloroform, and allowed to stand to obtain a light yellow powder. Yield 0.32 g. Melting point 178-183°C. Total yield 1.44 g (58%). This was recrystallized from isopropanol to obtain a light yellow acicular crystal (melting point 191-196°C). It had the following physical properties.

Infrared ray absorption spectra (cm^{-1}): 1600 (ν_{C-N}), 700 (phenyl)

Mass analysis (m/e, relative intensity): 249 (M^+, 100%)

NMR spectra (DMSO-d_6):

2.78 (3H, d, J = 5Hz, $NH\underline{CH_3}$),

5.55 (1H, bq, J = 5Hz, $N\underline{H}CH_3$),

7.00-7.52 (10H, m, phenyl proton),

10.67 (1H, bs, ring RH)

Elementary analysis ($C_{16}H_{15}N_3$):

Calculated value: C, 77.08; H, 6.09; N, 16.86

Measured value: C, 76.85; H, 6.11; N, 16.77

The crystal thus obtained was identified as 2-methylamino-4,5-diphenylimidazole.

Application Example 2

Preparation of 2-methylamino-4,5-diphenylimidazole hydrochloride

After catalytic reduction by the same manner as that in Application Example 1, 1.3 mL concentrated hydrochloric acid was added to the reaction solution, and this was filtered to remove the catalyst. Then the filtrate was concentrated and dried to a solid. The residue was

dissolved in 6 mL ethanol. supplemented with 25 mL ether, and kept cold for 3 days. The produced crystal was separated by filtering, washed twice with 2 mL ethanol-ether (1:10), and vacuum dried to obtain a colorless plate-form crystal (yield 0.81 g (28%), melting point 98-99°C).

Application Example 3

Preparation of 2-methylamino-4,5-diphenylimidazole nitrate

0.79 g raw material (3 mM) was reacted in the same manner as in Application Example 1. Concentrated nitric acid (61%, d = 1.38) 0.25 mL was added to the reaction solution, and after the catalyst was removed by filtering, the filtrate was concentrated and dried to a solid. Then 3 mL ethanol was added to the residue, and the resulting precipitate was separated by filtering to obtain a light yellow powder (yield 1.21 g (78%), melting point 155°C (decomposition)).

Application Example 4

Preparation of 2-methylamino-4,5-di(p-tolyl)imidazole

2.93 g 2-Methylamino-4-hydroxy-4,5-di(p-tolyl)-4H-imidazole•monomethanol salt (9 mM) and 1.20 g 5% palladium carbon were suspended in 50 mL methanol and catalytic reducing performed in the same manner as in Application Example 1. After the catalyst was removed by filtering, the filtrate was concentrated and dried to a solid. The residue was supplemented with 4 mL of 78% ethanol and kept cold for 6 h. The resulting precipitate was separated by filtering, washed twice with 1 mL of the same solvent, and air dried to obtain a light yellow columnar crystal (yield 1.46 g (58%), melting point 208-212°C). It was recrystallized from 78% ethanol to obtain a light yellow columnar crystal (melting point 209-217°C).

This crystal showed the following physical properties.

NMR spectra (DMSO-d_6):

2.25 (6H, s, $\underline{CH_3}$-C_6H_4-),

2.76 (3H, d, J = 5Hz, NH$\underline{CH_3}$),

5.44 (1H, q, J = 5.4Hz, N$\underline{H}CH_3$),

6.98 and 7.24 (4H and 4H, d, phenyl ring proton)

Elementary analysis ($C_{18}H_{19}N_3$):

Calculated value: C, 77.94; H, 6.91; N, 15.15

Measured value: C, 77.97; H, 6.95; N, 15.35

Application Example 5

Preparation of 2-methylamino-4,5-di(p-tolyl)imidazole hydrochloride

After 1.47 g of raw material (4.5 mM) with 0.60 g 5% palladium-carbon was reacted in 50 mL methanol in the same manner as in Application Example 4, 0.6 mL concentrated hydrochloric acid was added, and the catalyst was separated by filtering. Then the filtrate was concentrated and dried to a solid. The residue was dissolved in 4.0 mL of hot anhydrous ethanol and filtered. The filtrate was naturally cooled to room temperature and filtered to separate the precipitate. A light yellow prism-like crystal (yield 0.45 g (29%), melting point 128°C (foams)) was obtained.

And the mother liquor was concentrated, dried to a solid, dissolved in ethanol, and precipitated by adding ether to obtain a light yellow crystal (yield 0.38 g, melting point 113-128°C (foams)). Total yield 0.83 g (59%). The first crystal (the former) was recrystallized from anhydrous ethanol to obtain a product with melting point of 91°C (sinters) - 109°C (foams).
Mass analysis (m/e): 277 (M^+, 100%)

Application Example 6

Preparation of 2-isopropylamino-4,5-diphenylimidazole

1.11 g 2-Isopropylamino-4-hydroxy-4,5-diphenyl-4H-imidazole (3.8 mM) and 0.49 g 5% palladium-carbon were suspended in 50 mL methanol and catalytic reduction was performed in the same manner as in Application Example 1. The catalyst was removed by filtering, and the filtrate was concentrated to about 5 mL and allowed to stand. The resulting precipitate was separated by filtering, washed twice with 1.5 mL ethanol, and air dried to obtain a colorless acicular crystal (yield 0.67 g (64%), melting point 182-184°C). It was recrystallized from 78% ethanol to obtain a colorless acicular crystal (melting point 183-187°C).
Infrared ray absorption spectra (cm^{-1}): 1600 (ν_{C-N})
Mass analysis (m/e): 27.7 (M^+, 100%)
NMR spectra (DMSO-d_6):
1.17 (6H, d, J = 6.0Hz, $CH(\underline{CH_3})_2$),
3.70 (1H, m, $C\underline{H}(CH_3)_2$),
5.24 (1H, d, J = 8Hz, $N\underline{H}CH(CH_3)_2$),
7.05-7.55 (10H, m, phenyl proton)
Elementary analysis ($C_{18}H_{19}N_3$):
Calculated value: C, 77.94; H, 6.91; N, 15.15
Measured value: C, 78.03; H, 6.88; N, 15.18

Application Example 7

Preparation of 2-benzylamino-4,5-diphenylimidazole

0.34 g 2-Benzylamino-4-hydroxy-4,5-diphenyl-4H-imidazole (1 mM) with 0.14 g 5% palladium carbon was catalytically reduced in 10 mL methanol in the same manner as in Application Example 1. The catalyst was separated by filtering, and the filtrate was concentrated and dried to a solid. The residue was supplemented with 2 mL ethanol and allowed to stand at room temperature. The resulting precipitate was separated by filtering. It was washed once with 0.5 mL ethanol and air dried to obtain a lemon-yellow acicular crystal (yield 0.21 g (62%), melting point 205-207°C). This was recrystallized from ethanol to obtain a lemon-yellow acicular crystal (melting point 206-208°C).

Infrared ray absorption spectra (cm^{-1}): 1600 (ν_{C-N})

Mass analysis (m/e): 325 (M^+, 77%), 234 ($M^+-C_7H_7$, 80%)

NMR spectra (DMSO-d_6):

4.40 (2H, -d, J = 6.6Hz, $NHC\underline{H}_2$),

6.12 (1H, t, J = 6.6 Hz, $N\underline{H}CH_2$),

7.00-7.50 (10H, m, phenyl ring proton),

Elementary analysis ($C_{22}H_{19}N_3$):

Calculated value: C, 81.20; H, 5.89; N, 12.91

Measured value: C, 80.91; H, 5.86; N, 12.87

The compounds to be provided by the present invention show anti-inflammation activity, especially strong pain alleviating activity as shown by some examples below. In addition, wide physiological activities such as antiviral activity, antiallergy activity, immunity inhibition or acceleration, antiulcer activity, insect extermination activity, etc., are expected in the compounds provided by the present invention, and they are useful as medicines.

Reference Example 1

(Carrageenin edema method)

A physiological saline aqueous solution of 0.1 mL 1% carrageenin was hypodermically injected in right foot pads of SD type rats, and an increase in the volume of foot was measured after 3 h. The edemization rate was calculated.

A medicine was orally administered 1 h before carageenin administration.

The edemization inhibition rate was calculated by the following equation.

Edemization inhibition rate (%)

= [(edemization rate of control group) - (edemization rate of medicine administered group]/(edemization rate of control group) x 100

The results are shown in Table I.

Reference Example 2

(Acetic acid writhing method)

Physiological saline containing 0.8% acetic acid was injected at an administration quantity of 0.1 mL/10 g into the abdominal cavity of ICR system mice, and the writhing number was measured for 10 minutes after 10 minutes. A medicine was orally administered one hour before administration of acetic acid. The writhing inhibition rate was calculated by the following equation.

Writhing inhibition rate (%)

= [(writhing number of control group) - (writhing number of medicine administered group)]/(writhing number of control group) x 100

Results are shown also in Table I.

Table I

① 化合物	④ 投与量 (mg/kg)	⑤ カラゲニン浮腫抑制率 (%)	⑥ 酢酸ライジング抑制率 (%)
② 実施例1の化合物	25	11	68
② 実施例4の化合物	25	—	44
② 実施例6の化合物	25	22	36
② 実施例7の化合物	25	—	52
③ イブプロフェン	25	40	30

Key:
1 Compounds
2 Compound of application example
3 Ibuprofen
4 Administration quantity
5 Carrageenin edemization inhibition rate
6 Acetic acid writhing inhibition rate